REMARKS

Objection for alleged informalities:

Claims 164, 171 and 175 were objected to because of informalities. The instant Office Action states, "abbreviations ... should not be used in the claims without reciting the full terminology for which they are used unless they are common within the art," and adds "[a]ppropriate correction is required."

Applicants note that the Office Action fails to cite any statutory basis for this requirement, and further, Applicants note that the M.P.E.P. , section 2173.05(a), states:

"The meaning of every term used in a claim should be apparent from the prior art **or from the specification** and drawings at the time the application is filed. **Applicants need not confine themselves to the terminology used in the prior art, but are required to make clear and precise the terms that are used to define the invention whereby the metes and bounds of the claimed invention can be ascertained.** During patent examination, the pending claims must be given the broadest reasonable interpretation consistent with the specification. In re Prater, 415 F.2d 1393, 162 USPQ 541 (CCPA 1969). See also MPEP Section 2111 - Section 2111.01. **When the specification states the meaning that a term in the claim is intended to have, the claim is examined using that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art.** In re Zletz, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989)."

Applicants respectfully submit that the instant specification provides clear and precise definitions for the abbreviations used throughout the specification, but note that typographic errors were made during the preparation of the new set of Claims (Claims 162-182), supplied with the Response to Restriction Requirement, dated April 11, 2003. Consequently, Applicants have amended Claims 164, 171, 175 (and others containing protein name abbreviations) to correct the typographic errors and bring the abbreviations used in Claims into agreement with the abbreviations defined in the specification. For example, the abbreviation "IKKB" in the previously submitted Claim 164 has been amended to "IKKb," which is defined in Table 1 on page 5 of the specification as "IkappaB kinase beta", and further defined on page 23 of the specification by referral to GenBank accession no. AF031416. Applicants submit that, given the definitions presented in the specification, one of average skill in the art would understand what was

meant by the abbreviations used in the claims. Applicants further submit that to use the full names of the corresponding proteins, as suggested, would make the claims difficult to read, at best.

Applicants also note that the M.P.E.P. , section 2111.01, states:

"Applicant may be his or her own lexicographer as long as the meaning assigned to the term is not repugnant to the term's well known usage. In re Hill, 161 F.2d 367, 73 USPQ 482 (CCPA 1947)."

In view of these arguments, Applicants respectfully request that the Examiner's objection to their use of abbreviations in the pending claims be withdrawn.

Rejection for alleged omission of essential step:

Claims 164-166 and 169-172 were rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps.

Applicants have amended Claims 164 and 171 to include the step of "a determination of the amount of interaction of the first and second proteins in the absence of the test compound," as suggested by the Examiner. Applicants believe that the amended Claims 164 and 171 now provide the omitted essential steps and respectfully request that this rejection be withdrawn.

Rejection for alleged indefiniteness and alleged insufficient description:

Claims 170, 172 and 179 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention. Claims 170, 172 and 179 were also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the invention was filed, had possession of the claimed invention.

Applicants have cancelled Claims 170, 172 and 179, as well as Claims 163 and 181, thereby obviating rejection. Applicants therefore respectfully request that this rejection be withdrawn.

Rejection for alleged non-enablement:

Claims 164-166, 169-172, 175-176, and 178-179 were rejected under 35 U.S.C. 112, first paragraph, for allegedly not being enabled by the specification.

Applicants have discovered that IKKa, IKKb, IKKg and IKK-i specifically interact with previously unknown binding partners in the context of the yeast two-hybrid assay described in Example 1 of the instant application. As pointed out by the Examiner in the instant Office Action: "IKKa, IKKb, IKKg and IKK-i have well defined roles in the activation of the NFκB signal transduction system and the usefulness of modulators of the NFκB signal transduction system is well established in the art." However, the Examiner notes "the specification fails to show that any of the binding pairs claimed is physiologically relevant (i.e., occurs *in vivo*) during activation of the NFκB signal transduction system," and further notes that "there is no evidence that the binding of any of these pairs is in fact part of the NFκB signal transduction system."

Applicants respectfully submit that whether or not the previously unknown protein-protein interactions and protein complexes discovered by the inventors are "physiologically relevant," or even are "part of the NFκB signal transduction system," is not germane to the issue of whether the pending Claims are patentable. What is germane to patentability is whether the disclosed protein-protein interactions and protein complexes, and the screening methods making use of these complexes, are (a) novel, (b) non-obvious, and (c) useful. Applicants respectfully submit that perhaps the Office is having difficulty recognizing the usefulness, or utility, of the instant invention.

Applicants respectfully assert that the previously unknown interactions and complexes of the present invention are useful for screening for compounds that are **potentially** useful as modulators of IKKa, IKKb, IKKg or IKK-I function, and compounds selected by such screens are therefore **potentially** useful as modulators of the NFκB signal transduction system. Applicants stress that, when apprised of their invention, individuals skilled in the art of drug screening will be most definitely be enabled to develop novel screens for lead compounds that **potentially** modulate the NFκB signal transduction system.

Applicants note that the Examiner concludes her rationale for the instant rejection by stating "... one of skill in the art would have no expectation that any compounds which would be selected by the claimed methods would be useful for modulating the NFKB signal transduction system...." Applicants wish to remind the Examiner that **the pending claims are drawn towards methods for selecting modulators of isolated protein complexes** – protein complexes that all contain, as one of the two binding partners, either IKKa, IKKb, IKKg or IKK-i. Applicants stress that **the pending claims are NOT drawn towards methods for selecting modulators of the NFκB signal transduction system**, and therefore they should not be evaluated for their patentability based on that criterion. (Applicants note, however, that they hope some of the modulators of the disclosed isolated protein complexes revealed by the methods proposed in the instant application will turn out to be modulators of the NFκB signal transduction system.)

Applicants' assertions of utility for their invention, as defined by the pending claims, are based upon the following line of reasoning:

1. The yeast two-hybrid assay has revealed that the proteins IKKa, IKKb, IKKg and IKK-i make heretofore unknown interactions with specific proteins in the context of the yeast two-hybrid assay, and such interactions are at least stable enough to allow the reconstitution of a transcriptional activator within the nucleus of S. cerevisiae, leading to the generation of a signal.

2. As confirmed by the Examiner, (a) the proteins IKKa, IKKb, IKKg and IKK-i, have well defined roles in the activation of the NFκB signal transduction system, and (b) the usefulness of modulators of the NFκB signal transduction system is well established in the art.

3. Proteins, such as IKKa, IKKb, IKKg and IKK-i, are molecules having a defined 3-dimensional shape and a limited number of exposed surfaces that can be used for binding by partner proteins.

4. When specific interactions are made between IKKa, IKKb, IKKg or IKK-i and a particular partner protein (whether physiologically relevant or not), the interactions take place at a specific binding site or surface on IKKa, IKKb, IKKg or IKK-i.

5. Compounds that modulate the specific interactions made between IKKa, IKKb, IKKg or IKK-i and a particular partner protein (e.g., the binding partners disclosed in the instant application – whether physiologically relevant or not) have significant potential to modulate binding of other partner proteins that bind to IKKa, IKKb, IKKg or IKK-i through the same binding site or surface or any nearby site or surface that is allosterically affected by the modulating compound.

6. Therefore, **the compounds identified by the methods of the present invention embody a novel class of lead compounds that are potentially capable of modulating the NFκB signal transduction system**. These lead compounds can be used as the structural starting points for additional rounds of structural modification and experimentation, which will hopefully identify secondary compounds that are indeed effective modulators of the NFκB signal transduction system, and can be used for therapeutic purposes.

Applicants further assert, that, appraised of the instant invention, individuals of average skill in the art of drug screening can employ any of several well-known methods to screen for modulators of the protein complexes of the present invention. The compounds so identified, regardless of the screening method employed, represent lead compounds that have the potential to modulate the NFκB signal transduction system, and which warrant further investigation in appropriate NFκB signal transduction assays that are also well known in the art, and beyond the scope of the instant invention.
In view of these arguments, Applicants firmly believe that their application is enabling for one of average skill in the art of drug screening. Applicants therefore respectfully request that the enablement rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejection for alleged obviousness:

Claims 164-166, 169-172, 175-176, and 178-179 were rejected under 35 U.S.C. 103(a) as being unpatentable over Cao (U.S. Patent 5,776,717) or Akira et al. (WO 00/24908).

As noted in the instant Office Action, Cao teaches that a family of IKKs phosphorylate IκB on a specific regulatory serine residue, and that the KIA0151 gene product, which is also known as IKK-i, is a member of this IKK family that binds to

TRAF2. Cao further teaches a method to identify agents that modulate IκB kinase comprising mixing an IκB kinase, such as IKK-i with a binding target of the kinase, such as TRAF2, in the presence and absence of a candidate modulator. According to the instant Office Action "Cao do not specifically teach the selection of the KIAA0151 gene product as the IκB kinase and TRAF2 as the IKK binding target for use in the disclosed methods. However, the selection of these two proteins [i.e., KIAA0151 (a.k.a. IKK-i) and TRAF2] as the binding partners in the disclosed methods [of the instant application] would have been obvious to one of ordinary skill in the art...."

Applicants respectfully point out that the instant application does not disclose interactions between IKK-i and TRAF2, and furthermore, does not disclose screening assays based upon this interaction. The instant application does, however disclose interactions between IKK-i and PN13730 (Example 3, page 24), IKK-i and I-TRAF (Example 11, page 26), IKK-i and NUMA1 (example 12, page 26), and IKK-i and SPA-1 (example 13, page 26). Applicants respectfully assert that (a) I-TRAF is not TRAF2, and (b) the interactions formed between IKK-i and PN13730, I-TRAF, NUMA1, or SPA-1 could not have been predicted based upon the observation that IKK-i and TRAF2 interact. Therefore, the interactions formed between IKK-i and PN13730, I-TRAF, NUMA1, or SPA-1, and any screening assays based upon these interactions, would not have been obvious to one of average skill in the art.

Furthermore, the mere fact that the Examiner doubts the interactions between any of the protein pairs in the instant application, except perhaps for the interaction between IKK-i and I-TRAF, are "physiologically relevant (i.e., occurs in vivo)" (page 5 of the instant Office Action), indicates that it would not have been obvious to one of average skill in the art to use any of the protein complexes of the instant invention in the screening assay described by Cao.

For these reasons, Applicants respectfully request that the rejection under 35 U.S.C. 103(a) in view of Cao (U.S. Patent 5,776,717), be withdrawn.

Applicants acknowledge that Akira et al. teach that IKK-i "specifically interacts with I-TRAF," and further, that epitope tagged fusion proteins of the two proteins can be co-immunoprecipitated and used in assays to screen for modulators of this interaction. Applicants therefore amend claims 162, 164, 171, 175, 178, 180 and 182 to specifically

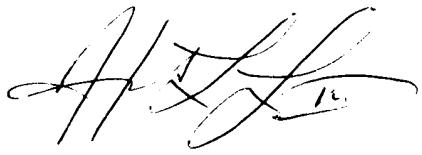
exclude isolated protein complexes or protein-protein interactions comprising IKK-i, an IKK-i fragment or a fusion protein containing IKK-i or an IKK-i fragment as a first protein interacting with I-TRAF, an I-TRAF fragment or a fusion protein containing I-TRAF or an I-TRAF fragment as a second protein. Applicants believe that these amendments obviate the rejection, making the rejection based upon the teachings of Akira moot. Applicants therefore respectfully request that the rejection under 35 U.S.C. 103(a) in view of Akira et al. (WO 00/24908), be withdrawn.

In accordance with 37 C.F.R. 1.121(f), Applicants submit that none of these requested amendments adds new matter to the Application.

CONCLUSION

Applicants believe that once the amendments proposed above have been incorporated into the pending claims, the pending claims will be in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned to expedite allowance of this application.

Respectfully submitted,



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Michael Moreno

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